REMARKS

Sequence Listing

This Response complies with the requirements for patent applications containing nucleotide sequence and/or amino acid sequence disclosures. Applicants enclose herein the Sequence Listing, the Computer Readable Form of the Sequence Listing, the Compliance Statement concerning the aforementioned Sequence Listing, and a copy of the Notice to Comply with Requirements for Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures. Applicants believe no fees are due, however, should this be in error, please debit Deposit Account No. 07-1185 on which the undersigned is allowed to draw.

The 35 U.S.C. §112 Rejection

Claims 1-7 and 16-22 were rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. The rejection is respectfully traversed.

The Examiner argued that the effects of modifying the fiber knob of an adenovirus on the folding/binding properties of the protein are not predictable. However, Applicants submit that the

lengths of the HI loop of the fiber knobs in different adenovirus serotypes vary significantly, indicating that alterations of the original structure of the loop, such as insertions and deletions, should be compatible with the correct folding of the entire knob domain (instant specification, page 25, lines 3-15). In the reference of **Wickham** et al. cited by the Examiner, it was disclosed that the crystal structure of the fiber knob is known, and there are conserved and non-conserved amino acids that are and are not respectively involved in forming the proper fiber protein secondary structure (column 7, line 49 to column 8, line 2). The corresponding residues important in the fiber knob for protein binding/folding appear to be conserved between different adenoviral serotypes, and those regions that are not critical for the fiber protein folding can be mutated by insertion of a ligand (**Wickham** et al., column 8, lines 15-34). Therefore, Applicants submit that there is sufficient information available to one of skill in the art to insert a ligand into the loop regions of the fiber protein without causing significant changes to the folding/binding of the fiber protein.

Claim 1 has been amended to recite an adenovirus that mediates enhanced gene transfer to primary tumor cells, wherein

the fiber gene of said adenovirus is modified by introducing a ligand into the HI loop domain of the fiber knob. Insertion of a peptide motif containing the RGD sequence or the FLAG peptide was disclosed as example of modifying the fiber gene by insertion into the H1 loop. Enhanced gene transfer to primary tumor cells was demonstrated with ovarian cancer cells obtained from patients (page 97, line 12 to page 98, line 8, Figure 17; page 100, line 20 to page 101, line 11, Figure 19), primary tumor explants (Example 29, Figure 20) and primary explant of human SCCHN cells (Example 33, Figure 25). These data indicate the modified adenovirus can mediate significant enhancement of gene transfer to primary tumor cells through a coxsackievirus and adenovirus receptor-independent pathway. Hence, Applicants respectfully submit that the scope of the claims 1-7 in the instant application has a reasonable correlation to the scope of the enablement provided. Accordingly, Applicants respectfully request that the rejection of claims 1-7 under 35 U.S.C. §112, first paragraph, be withdrawn.

Claim 16 has been amended to recite a method of increasing the ability of an adenovirus to transduce primary tumor cells by introducing a ligand into the HI loop domain of the fiber knob of said adenovirus. As discussed above, the specification has

demonstrated enhanced gene transfer to primary tumor cells such as ovarian cancer cells obtained from patients (page 97, line 12 to page 98, line 8, Figure 17; page 100, line 20 to page 101, line 11, Figure 19), primary tumor explants (Example 29, Figure 20) and primary explant of human SCCHN cells (Example 33, Figure 25) by adenovirus modified with a ligand inserted into the H1 loop. Applicants respectfully submit that the scope of the claims 16-22 in the instant application has a reasonable correlation to the scope of the enablement provided. Accordingly, Applicants respectfully request that the rejection of claims 16-22 under 35 U.S.C. §112, first paragraph, be withdrawn.

Claims 9-15 and 23 were rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. The rejection is respectfully traversed.

Claim 9 has been amended to recite an adenovirus of the present invention further comprises a herpes simplex virus-thymidine kinase gene. Claim 11 is drawn to a method of using the virus of claim 9 and ganciclovir to kill tumor cells in an individual. Applicants submit that the method of administering adenovirus that carries herpes simplex virus-thymidine kinase gene to an individual

followed by ganciclovir treatment is a standard treatment procedure that is currently used in a number of gene therapy trials. Hence, it does not require undue experimentation for one of ordinary skill in the art to practice this method of killing tumor cells. Accordingly, Applicants respectfully request that the rejections of claims 9-15 and 23 under 35 U.S.C. §112, first paragraph, be withdrawn.

Claims 13-23 were rejected under 35 U.S.C. §112, second paragraph, for omitting essential steps. The rejection is respectfully traversed.

Claim 16 has been amended to recite the step of transducing tumor cells with the modified adenovirus that results in enhanced gene transfer to primary tumor cells. Accordingly, Applicants respectfully request that the rejections of claims 13-23 under 35 U.S.C. §112, second paragraph, be withdrawn.

The 35 U.S.C. §102 Rejection

Claims 1-9, 16-20 and 23 were rejected under 35 U.S.C. §102(e) as being anticipated by **Wickham** et al. The rejection is respectfully traversed.

Wickham et al. disclosed an adenovirus modified by insertion of a ligand into the C-terminal of the fiber knob. However, **Wickham** et al. did not teach or suggest that such a modified adenovirus could mediate or result in enhanced gene transfer to primary tumor cells.

Claims 1-9 in the instant invention are drawn to a modified adenovirus that mediates enhanced gene transfer to primary tumor cells. Claim 16 is drawn to a method of using such modified adenovirus to enhance gene transfer to primary tumor cells. As discussed above, the present invention provides data that show the claimed adenovirus mediates enhanced gene transfer to primary tumor cells (Figures 17, 19, 20, 25). Generation of a modified adenovirus that mediates enhanced gene transfer to primary tumor cells and the method of using such modified adenovirus to enhance gene transfer to primary tumor cells were not taught or suggested in **Wickham** et al. Hence, **Wickham** et al. does not anticipate claims 1-9 and 16-20, and the present invention is different and distinct from **Wickham** et al. Accordingly, Applicants respectfully submit that the rejection of claims 1-9, 16-20 and 23 under 35 U.S.C. §102(e) be withdrawn.

This is intended to be a complete response to the Office Action mailed April 10, 2000. If any issues remain outstanding, the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

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